

EXHIBIT B

European Patent No. 764 447
(Application No. 96114439.1)

Bayer Corporation

Opposed by Baxter Healthcare Corporation

**Counter-response by the Opponent
to the Proprietor's response to the opposition**

10 October 2005

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1. REQUESTS

Our requests remain the same as in the notice of opposition.

2. LACK OF INVENTIVE STEP

2.1 SUMMARY OF OPPONENT'S POSITION

5 Firstly, we maintain our position that the claimed subject matter is completely obvious over a combination of D1 and D2. The proprietor's comments and, indeed, some of the features of the claim (for example, the duration of the incubation) are simply an attempt to distract attention from this basic fact. We are submitting further documents to show that the claim represents an obvious
10 combination of the processes of D1 and D2 and that any features of the claim that are not explicitly disclosed in D1 and D2 do not contribute any technical effect. A further, newly cited, document (D6) discloses a combination of the D1 and D2 processes, anyway.

Secondly, we show that the patent made no contribution to the art.

15 Thirdly, we show that the apparent claim scope is not commensurate with the disclosure of the Examples, nor with the arguments that the proprietor has put forth in support of the patent.

Fourthly, contrary to the impression that was given by the patent proprietor, we do not seek to contest the results that are presented in the opposed patent. More specifically, the experimental report that we submitted as D4 was not intended to show that the results in the patent were erroneous. Instead, it shows that the
20 current EPO claim purports to cover processes in which the ACA level is not raised during the solvent-detergent step (step (a) of the claim) and therefore that *the claim lacks the technical features that are necessary in order for a problem to be solved*. If the proprietor wishes the Opposition Division to take note of his
25 arguments concerning the differences between the process in the patent and the process disclosed in D4, then claim 1 should be amended so that it is restricted to the allegedly different process of the invention.

2.2 CLAIM 1 LACKS AN INVENTIVE STEP OVER A COMBINATION OF D1 AND D2

30 In our original opposition, we took D2 as the "closest item of prior art" and showed that it was obvious to use the solvent-detergent method of D1 in order to

reduce viral titre in the D2 product. The proprietor's position (section 2.1 of the response) is that we have identified the wrong problem to be solved. In his submission, D1 should be taken as the closest item of prior art and the problem to be solved was the reduction of anticomplement activity (ACA). Although we
 5 maintain our position that D2 can be regarded as the closest item of prior art and the problem is then to reduce viral titre, we are equally prepared to regard D1 as the closest item of prior art, in which case the problem to be solved is then, as the proprietor acknowledges, the reduction of anticomplement activity.

D1 discloses that the solvent-detergent process can be applied to any composition
 10 that contains blood proteins. In particular, as is set out at column 7, lines 9 to 26, the process can be applied to the sort of blood fractions that are disclosed in the table in column 6, including fractions II and III (which contain immunoglobulins IgG, IgM and IgA). IgM is specifically mentioned again at column 7, line and 26. It is clear, therefore, that the D1 process is disclosed as being applicable to
 15 preparing solutions of antibodies and it appears that the proprietor does not contest this.

The problem is then to reduce anticomplement activity. We refer the opposition division to D2, column 2, lines 21-23:

20 *"Incubation of gammaglobulin at pH 4.0 at 37°C for various lengths of time has been observed to reduce the anticomplement activity to low levels."*

Moreover, at column 4, lines 33 to 34, D2 also discloses that *"the ionic strength of the solution is reduced"*. At column 6, lines 46 to 47, it is more specifically stated that the ionic strength is preferably less than about 0.001.

25 Hence, referring to step (c) of the opposed claim, the pH is within the range disclosed in D2, the temperature is within the range disclosed in D2 and the ionic strength is precisely what was disclosed already as being preferable in D2.

The only remaining parameter is the incubation period of at least 10 days. The precise period of incubation is not stipulated in D2 and the duration of the
 30 incubation in Example 1 of D2 (column 8 line 65 to column 9 line 12) is not disclosed. The person skilled in the art, wishing to put D2 into practice would simply and routinely try different incubation times in order to achieve the desired reduction in ACA. This would not have involved an inventive step.

Hence, the opposed patent claim represents simply:

- 35
- the D1 process, applied to antibody solutions, as was already taught in D1,
 - followed by the D2 low pH incubation step in order to reduce ACA (as taught in D2), with
 - the precise incubation period being arrived at by routine experimentation.

The subject matter of claim 1 therefore lacks an inventive step.

2.3 CLAIM 1 LACKS AN INVENTIVE STEP OVER A COMBINATION OF D1 AND D2, IN THE FURTHER LIGHT OF D5

In case the opposition division does not agree with our submission above, namely that suitable incubation periods would have been determined by means of routine, non-inventive, trial-and-error experiments, we submit that D2 adequately identified references that would enable the person skilled in the art to select suitable incubation periods. More specifically, D2, at column 2, lines 26 to 50, contains various references to documents that were disclosed in D2 specifically in the context of a "pH 4.0 gammaglobulin" product having low ACA.

For example, see the Barandun *et al* (1962) *Vox Sang.* reference that is cited at D2, column 2, lines 37 to 38, which we now submit as D5. On page 165, there is a table showing the results of incubating a gammaglobulin preparation for differing times at differing pHs. All of the experiments were conducted at 37°C. It can be seen that, at pH 4, an incubation time of only about three hours is necessary to reduce ACA to an optimal value. Further down that page, the authors address the effect of temperature. They tried incubating the preparation at 20°C and 4°C and found that it was only partially effective over the sorts of timescales with which they appear to have been working, namely up to about a day. They concluded that the optimal conditions for the incubation were "*between pH 3.8 and 4.0 and 24 hours incubation at 37°C.*" (last few lines of page 165).

All that the patent proprietor seems to have done is to deliberately pick a suboptimal incubation temperature (namely 22°C or 5°C; see page 7, line 6, of the granted patent), such that the incubation period has to be extended in order to compensate for the lower temperature. It can be seen from Table 5 on page 7 of the patent, in the section entitled "Final Incubation", that there was a greater reduction of ACA when the sample was incubated at 22°C for 21 days than when it was incubated at only 5°C for 21 days. The inventors conclude (page 7, lines 24 to 25) that "*the reduction in ACA is dependent on temperature, with faster reduction in ACA observed at high temperatures*". The observation that the reduction of ACA depends on temperature contributes nothing to the prior art, since it does not go beyond the information that is on page 165 of D5, published as long ago as 1962.

The Opposition Division may wonder why a patent that is restricted to unnecessarily long incubation periods should be of concern to an opponent who, presumably, could operate the process at the optimal temperature of 37°C (as identified in D5) and thereby reduce the incubation period to well below the minimum level of 10 days that is specified in the opposed patent claim. It is important for the Opposition Division to appreciate three things.

- Firstly, although the *results* in the patent relate to incubations at suboptimal temperatures, the *claim* covers incubations that are conducted at from 2 to 50°C, hence embracing the optimal temperature of 37°C that was already identified in D5.
- 5 • Secondly, although the *results* in the patent relate to incubations for prolonged periods, the *claim* is not restricted to processes in which the reduction of ACA is only achieved *after* the minimum period of 10 days (or, indeed, as a result of the low pH incubation step at all); at least in terms of its literal scope, the EPO claim purports to cover a process in
10 which a satisfactory reduction of ACA might be achieved within a matter of hours but the composition is then simply held under the same incubation conditions for a more prolonged period, during which ACA is not materially further reduced.
- 15 • Thirdly, there was another reason, taught in the prior art, for concluding the process with a low pH incubation step, namely to reduce viral titre. We address this aspect in section 2.10 below.

It should be noted that, at column 9 lines 15 to 20, D2 teaches just such a prolonged maintenance of the preparation, namely for “stability and other testing” (line 16) and simple storage (line 20). The ionic strength was not increased and
20 nor was the pH raised, presumably because neither of these steps was necessary. In the general description of the D2 invention, at column 4, lines 38 to 41, it is stated that

25 *“The pH and ionic strength are maintained at the above levels during protein concentration adjustment, sterilization, filling into final containers, and the like.”*

And, at lines 53 to 56 of the same column, it is stated that

“The material may be kept at room temperature for long periods in the absence of additives with retention of its monomer content and lack of actual and latent anticomplement activity.”

30 Clearly, “long periods” will be more than 10 days.

Those in this field should be free (i) to carry out a D5-style incubation in order to reduce ACA and then (ii) to keep the resulting solution under the same conditions for an indefinite period thereafter as is taught in D2 without being forced to take the unnecessary step of raising the pH or increasing the ionic level merely in order
35 to avoid a patent claim that extends far beyond any possible contribution to the art.

Hence, Claim 1 represents an obvious combination of D1 and D2 in the further light of cross-referenced D5.

Furthermore, there was another prior art reason for carrying out a low temperature incubation, which is explained in more detail in the next section of our submission.

2.4 CLAIM 1 WAS OBVIOUS OVER D6

5 We wish to introduce D6 (Prince *et al*, 1988) into the proceedings. Overall, it should be regarded as the "closest item of prior art", since it discloses a combination of the SD and low pH incubation treatments for an antibody solution.

10 More specifically, it discloses, under the heading "Materials and Methods" on the first page, a process for preparing an immune globulin composition, which is therefore clearly an "antibody solution", as required by Claim 1. A purified gammaglobulin fraction was treated with TNBP and Tween 80, which are, respectively, the preferred solvent and one of the two preferred detergents in the opposed patent; see claim 15. Step (a) is therefore disclosed in this reference.

15 Next, "*to prepare intravenously tolerable immunoglobulin the globulin was held at pH 4.1 for 21 hr at 37°C in the presence of 350 units of pepsin per gram of protein*". Except for the fact that this particular incubation was for less than 10 days and the ionic strength is not explicitly disclosed, this passage therefore discloses step (c) of the opposed claim. We note that the pH 4.1 step was specifically utilized for the purpose of making the preparation suitable for intravenous administration. This is precisely the reason that the patent proprietor includes step (c) in the opposed process.

25 From the sentence bridging pages 6944 and 6945, it can be seen that the resulting product had low viral activity. D6 does not report any adverse reactions. The lack of adverse reactions indicates that the product had a low level of anticomplement activity and, as noted above, the low pH incubation was employed specifically to make the composition "intravenously tolerable". In addition, the product was being tested for use in humans. Moreover, Table VI of D5 can be taken as "expert evidence" that the 21 hour incubation at 37°C that is disclosed in D6 will have achieved the same effect as a longer incubation at a lower temperature. Hence, for any and all of these reasons, it can be presumed that the product intrinsically had low ACA.

35 In the light of the well-established practice (exemplified by D5) of incubating IVIG solutions at a low pH and low ionic strength to make them intravenously tolerable (by lowering ACA), it is furthermore the case that the person skilled in the art would have known that this step in D6 would have achieved this effect.

It should be noted that D6 does not disclose any additional processing step following the low pH incubation. It can be presumed, therefore, that the solution was allowed to cool to room temperature and was then kept until it was used. (The very low amount of pepsin that was used in the incubation would not need

removing.) Hence, since the opposed claim does not indicate that the low ACA is only achieved *after* at least 10 days have passed, simple storage of the solution obtained in the D6 process could be regarded as constituting a prolonged incubation of the sort set out in step (c) of the claim.

- 5 In relation to the ionic strength, which is not explicitly disclosed in D6, we note that the patent contains no results to show that the low ionic strength contributes any unexpected technical effect to the claimed subject matter. Instead, as is acknowledged at lines 15 to 16 on page 2 of the opposed patent, the low ionic strength of the solution has been picked for prior art reasons, namely on the basis
10 of the disclosure of the "Tenold '608 process", which is D2 in these present proceedings. Specifically, D2 disclosed at column 4 lines 33-38 that the ionic strength was low in order to increase the monomer content of the preparation and to reduce ACA.

- The only remaining feature of the claim is step (b), namely the removal of the
15 TNBP and detergent. As is acknowledged in the opposed patent at page 4 lines 15 to 17, one would not wish these materials to remain in the product. In fact, the removal of TNBP and detergent, although not specifically mentioned in D6 (which does not disclose every detail of the preparative process, since it is more concerned with the potential of the product to neutralise HIV than the production
20 process itself), is an integral part of the commercial process that is known as the 'solvent detergent' viral inactivation process, as taught by D1. For example, see column 9, lines 19 to 51, of D1, which indicates that "*Normally, after the treatment, the trialkylphosphate and other inactivating agents, for example, ether, are removed*". D7 (Eriksson *et al*, 1994) constitutes further proof that the solvent
25 and detergent are removed from intravenous products after the SD process step; see page S39, right-hand column, 14 lines after the heading "*Virus inactivation in the manufacture of immunoglobulins*":

"The solvent and detergent are removed from the immunoglobulins by oil extraction and CM-Sepharose chromatography"

- 30 Hence, it can be presumed that these agents were, in fact, removed in the D6 process, in accordance with normal practice at the time. Alternatively, since it was common general knowledge by the priority date of the opposed patent that, following an SD step, the solvent and detergent should be removed, it was obvious to introduce a removal step. (If the proprietor contests that removal of the solvent
35 and detergent was common general knowledge, we can provide further evidence, but it seems unnecessary to do so.)

- Hence, at most (and without conceding that there is any significant difference between D6 and the opposed claim), the only *potentially* significant difference
40 between claim 1 of the opposed patent and D6 is the ten day incubation period in the claim. However, in the light of the expert evidence provided by D5, it is clear that the longer incubation time specified in the claim has no technical effect, since the 21 hour incubation at 37°C in D6 already reduces ACA to a low level. As was

noted above, all that the proprietor has done in the Examples is to pick a sub-optimal temperature and then compensate for that by having a longer incubation time.

Therefore, Claim 1 lacks an inventive step over (i) D6, (ii) the common general knowledge (exemplified in D1 and D7) that the solvent and detergent would be removed and (if necessary) (iii) the disclosure in D2 that a low ionic strength solution should be used for the low pH incubation. The subclaims also lack an inventive step over D6, for the reasons set out on pages 7 and 8 of our original opposition.

10 2.5 CLAIM 1 WAS OBVIOUS OVER D10

D10 (EP 525 502) is quite similar to D6, in that it discloses the production of intravenously injectable immunoglobulins (Col. 1 lines 2-3) by means of the solvent-detergent method (Col. 3 lines 10-11) and a low pH incubation (Col. 3 lines 21-27). As in the case of D6, the duration of the incubation is shorter than is specified in the opposed claim but, as we noted above, this is because the incubation was carried out at 37°C, instead of the 5°C or 22°C exemplified in the patent. Hence, as was demonstrated in D5, the longer incubation of the patent is simply unnecessary. The ionic strength of the solution in the incubation step is not stated but, as noted above, the use of low ionic strength in this step was taught in D2 and in any case it has not been demonstrated by the patentee to contribute to the solution of any problem.

The OD should also note the passage at Column 3 lines 28-36 of D10. Here, the pH is adjusted to between 5.0 and 5.5 (and thus overlaps with the range of 3.5-5.0 specified in the opposed claim) and then, following steps that would not change the pH (e.g. addition of maltose and filtration), the solution is stored. Clearly, in the context of a commercial product, the storage period will be at least 10 days. Hence, although this storage is not explicitly disclosed in D10 as a functional step, it nevertheless constitutes an incubation as defined in step (c) of the opposed claim.

The point of our citing D10 as well as D6 is that D10 explicitly discloses, between the SD step and the low pH incubation step, the removal of the solvent and detergent; see Col. 2 lines 23-26. The removal step employs a hydrophobic chromatography step (Col. 2 lines 25-26 and Col. 3 lines 20-21), just as in the opposed patent (p.4 lines 32-34).

The tonicity of the product that resulted from the low pH incubation in D10 was adjusted with maltose (Col. 3 lines 23-24), just as in the patent (Claims 9 and 10), and was then suitable for intravenous injection (Col. 3 lines 37-38). It can therefore be deduced that it had a low ACA. Moreover, D10 (which was filed by the company Octapharma) appears to disclose the process for manufacturing the "Octagam" IVIG product, information concerning which is given in document

D14, which we address in the next section of this submission. As we show therein, the ACA of the product falls within at least claim 2 of the opposed patent and this constitutes further proof that the product of the D10 process would have had the “low anticomplement activity” specified in claim 1.

5 **2.6 CLAIM 1 WAS OBVIOUS OVER D14, OPTIONALLY TOGETHER WITH D5 AND/OR D2**

D14 is some publicity information concerning the “Octagam” IVIG product. As can be seen from the penultimate page, the brochure was published in February 1995, i.e. before the priority date of the opposed patent.

- 10 The product is clearly suitable for intravenous use and had, in fact, been used in patients since 1993. It can be presumed, therefore, that it had low ACA but this is confirmed on page 4 of the brochure, in any case.

15 The process scheme set out on page 7 shows an SD virus inactivation step, removal of the SD reagents and then a pH 4 treatment step. Hence, the only differences between opposed claim 1 and the *explicit* disclosure of D14 are the duration and ionic strength of the pH 4 incubation. As noted above, the technical contribution of these particular parameters in claim 1 (if any), beyond what was known in the prior art, has not been established by the patentee. Given that the Octagam product was already clinically acceptable, it is difficult to discern any contribution to the art made by the claimed subject matter. In addition, suitable incubation times were disclosed in D5 and the advantage of having a low ionic strength was disclosed in D2. Hence, even if these parameters in the D14 process were not publicly known (which we do not admit), it would have been a simple and routine matter for the person skilled in the art to replicate the D14 process in order to arrive at the claimed process.

25 On page 15, D14 confirms that the product may be stored for up to 2 years, which confirms our statement in section 2.5 above that the final storage (at pH5.0-5.5) would be done for at least 10 days.

30 Additionally, as D15, we submit the results of an analysis of the “Octagam” IVIG product, carried out in August 1995. Hence, the analysis relates to the product that was on the market before the priority date of the patent. It can be seen that the ACA was 47.6 CH₅₀ units/ml, and thus falls within the definition in claim 2. The solution contained 5% protein (2.5g in 50ml), which complies with claims 3 and 4. The ACA activity of 47.6 units is not materially different from the level of 45 units given in claim 3. In addition, in relation to all of claims 2 to 6, it should be noted that the claims are process claims, rather than claims to a product *per se*. All of these claims are dependent on claim 1 but there is no indication of the changes that must be made to the basic process of claim 1 in order to arrive at these differently-defined products. Hence, the claims do not contain a technical feature that can contribute an inventive step.

In claim 7, at least 99% of the antibodies are said to be monomeric. In the analysed Octagam product, the antibodies were 92.63% monomeric. As in relation to claims 2 to 6, claim 7 does not define the particular process parameter or parameters that must be selected in order to arrive at a 99% monomeric product. Hence, the claim does not contain a technical feature that can contribute to an inventive step.

On page 4 of D14, it is stated that the product has "normal osmolality" and, on page 7, it is indicated that the final product is prepared with maltose. Hence, the features of claims 8 to 12 are disclosed in D14.

D16 is a copy of the product information for "Octagam" IVIG, extracted from the Octapharma web site in August 2005. D16 shows that the solvent in the SD step was TNBP, which is the solvent specified in Claim 15. The detergent was Triton X-100, rather than either of the detergents specified in Claim 15, but the patentee has not shown any inventive significance for choosing polysorbate 80 or sodium cholate for the detergent, as opposed to the Triton X-100 that was used to prepare "Octagam" IVIG. In addition, as noted in the Notice of Opposition (page 8), the use of polysorbate 80 was disclosed in D3 and the use of sodium cholate was disclosed in D1. Hence, the subject matter of claim 15 was obvious.

We accept that the D16 website page has not been shown to have been published before the priority date. However, it will be evident to the opposition division from the information that is given in D16 that the process for preparing "Octagam" IVIG could not have changed, to the extent of using a different solvent in the SD step, between the product being launched in 1993 and the date of the website information, in 2005. Such a radical change in the manufacturing process of a biological product such as IVIG would require the product to be identified differently. See also the passage bridging pages 2 and 3 of D16 relating to the pharmacovigilance study that has been running since 1995. Clearly, the product must have remained the same during this period.

2.7 LACK OF INVENTIVE STEP OVER D11

We wish to introduce into the proceedings new document D11 (Ng *et al*, 1993). This disclosed the preparation of immunoglobulin M solutions for intravenous injection. The subject matter of Claim 1 can be seen in the main paragraph in the left-hand column on page 82. More specifically:

- an immunoglobulin solution was treated with TNBP and Tween 80, which are the favoured trialkylphosphate solvent and detergent of the opposed patent (see Claim 15), in order to achieve an at least 4log reduction in viral titre (see last sentence on page 83),
- "*Residual reactants from the viral inactivation step were removed...*",

- the solution was diafiltered against 0.0025 M Na acetate, pH 4.25,
- it was then formulated in 10% maltose and "... held at 25°C for 21 days prior to storage at 2-10°C".

5 A 0.0025M sodium acetate solution has a low ionic strength. It may not have an ionic strength of less than 0.001 (as is required in the opposed claim) but

- there is nothing in the patent to suggest that reducing the ionic strength from the already low level of D11 to less than 0.001 provides for a surprising technical advantage, and
- 10 • D2 (at Col. 6 lines 46-47) had already taught that keeping the ionic strength below 0.001 was advantageous in the final storage of IVIG solutions.

Hence, claim 1 lacks an inventive step over D11 alone or, alternatively, in combination with D2.

15 The resulting product was not tested for the parameters specified in claims 2 to 7. However, since the process was so similar to the process specified in claim 1, it can be presumed that the product was comparable and the onus is on the patentee to show otherwise.

20 The addition of the maltose was clearly intended to make the solution isotonic and would not have altered the ionic strength of the solution. Hence, claims 8 to 10 do not add a distinguishing feature.

As was noted in the Notice of Opposition (top of page 8), a 10% maltose solution has an osmolarity of about 294. Hence, claims 11 and 12 also do not further distinguish the subject matter from D11.

25 As noted above, the materials used in the SD step are as specified in claim 15. The pH was 4.6 to 4.8, which falls within the range specified in claim 16.

Hence, at least claims 1 to 12, 15 and 16 lack an inventive step over D11, either taken alone or in combination with D2.

Claims 13 and 14 also lack an inventive step over a combination of D11 and D2 for the reason given in our Notice of Opposition, top of page 8.

30 2.8 THE PRESENCE OR ABSENCE OF AGGREGATES FOLLOWING THE SD STEP IS IRRELEVANT

The proprietor has suggested that, at least in his particular solvent-detergent process, the ACA is raised even though aggregates are not encountered, whereas those in the art thought that aggregates were associated with a raised ACA.

Therefore, according to the proprietor, it was not obvious to use the D2 method in order to reduce ACA. However, the proprietor was careful (towards the end of page 2) only to say that "aggregation of antibodies causes high ACA". Quite correctly, he has never actually alleged that high ACA was considered to be
 5 *uniquely* associated with, or caused by, aggregation of antibodies. Hence, as a matter of logic, it does not follow that the (alleged) absence of aggregates in the proprietor's version of the SD step would have dissuaded the person skilled in the art from using a D2-type incubation in order to reduce ACA.

See, for example, D12 (Rousell et al, 1989), which is a paper emanating from associated and/or predecessor companies of the present patent proprietor. In the
 10 middle of the left-hand column on page 144 it is stated that:

"It is axiomatic, therefore, that an appropriate test for AC activity is included in the quality assurance battery required for release of the different intravenous immunoglobulin preparations."

15 And, a few lines further on, the authors refer to

"an intravenous immunoglobulin rendered safe for intravenous infusion by stabilisation at pH 4.25".

The authors then set out various assays for ACA. They do not test for aggregates. It is clear, therefore, that those in the art recognised that they needed to test the
 20 preparations for ACA and, if the ACA was too high, they needed to introduce a step (for example, a low pH incubation) in order to reduce the ACA. However, they did not need to test for aggregates.

Significantly, the proprietor has submitted no evidence to show that the person skilled in the art, having encountered a raised ACA following the solvent
 25 detergent step, would assay the preparation in order to see whether aggregates were present. Indeed, if the proprietor is correct to state (section 2.1 of the response, four lines from the end of page 2) that those in the art necessarily associated a raised ACA with the presence of aggregates, assaying for aggregates would have been a completely pointless step. Instead, the person skilled in the art
 30 would simply seek to reduce the ACA by carrying out the low pH incubation that was taught for that purpose in D2 and he would be completely unconcerned about whether aggregates had originally been present and were the cause of the (actual or presumed) high ACA. The person skilled in the art would simply wish to be satisfied that the low pH / low ionic strength incubation was achieving the effect
 35 taught in D2, namely the reduction of ACA.

D6 shows that, following an SD step to reduce viral contamination, those in the art would have routinely ended the process with a low pH and low ionic strength incubation *"to prepare intravenously tolerable immunoglobulin"* (D6, five lines from end of Col 2 on first page). There is nothing to suggest that the person

skilled in the art would have looked for aggregates since D6 shows that the use of this sort of incubation to lower ACA was a normal precaution in any case.

Alternatively, as we pointed out in our original opposition (section 2.1), it was obvious to improve upon the D2 process for preparing, and storing, IVIG solutions by adding an earlier SD step in order to reduce viral contamination. D6 is evidence that we were right: it was obvious, and it had already been done.

The patent proprietor's assertions concerning aggregates are merely a theory as to the formation of ACA and should not allow the proprietor to re-claim what was already in the public domain, namely the combination of the known viral inactivation step of solvent detergent with the known pH 4 method of ensuring that the resulting immunoglobulin preparation is administrable intravenously.

2.9 WE DO NOT (CURRENTLY) CONTEST THE DATA IN THE PATENT

2.9.1. *D4 was not intended to contradict the results in the patent*

In section 2.2 of the response to the opposition, the patent proprietor has suggested that the experiments that we reported in the D4 document were submitted in order to "challenge" the experiments reported in the patent. In section 2.4, he asserts that the D4 data do not "contradict" the data in the patent because the D4 data do not adequately reflect the experimental conditions that were used in the patent. In both of these sections, the proprietor's response might have been relevant if this part of our opposition had been filed under Article 100 (b) EPC. It was not. It was filed under Article 100(a), with reference to inventive step.

At least at present, we do not wish (or need) to contest the data in the patent, although we reserve the right to do so in the future. We will accept, purely for the sake of the present argument, that there may be particular ways of carrying out the solvent detergent step that do, in fact, raise ACA. The point of the D4 document was to show that there are *also* ways of carrying out the solvent detergent process that do *not* result in significantly raised ACA. Nevertheless, the person skilled in the art would wish to keep the resulting composition at a low pH and low ionic strength since these conditions were taught in the prior art (e.g. D2) as being suitable to *maintain* a low ACA. The issue is that, at least if read literally, the opposed claim does not specify that the ACA is raised in step (a) and is then reduced in step (c). The patent proprietor might (unjustifiably) try to assert the patent against someone operating a process in which ACA is low *throughout* the process. Such process would still "produce the antibody solution having low viral activity and low anticomplement activity" (see end of Claim 1), because the viral activity was already low or had been reduced in step (a) and the anticomplement activity had been low throughout. However, if read in such a way, the claim would not solve the problem that it purports to solve, because the problem would not be there in the first place.

For example, see D13 (which was published before the priority date). Referring to column 5, lines 28 to 30, one half of a batch of the IVIG solution was subjected to a solvent-detergent process and the other half was not subjected to this process. It can be seen from Table 5 in that column that there was no significant difference in the ACA level between the two preparations. In other words, D13 provides the direct comparison that the proprietor (at section 2.7) states is not provided in the D4 document that we previously submitted.

See also D8 (Pehta, 1996), which is a post-published document that we are citing as *expert evidence* of the fact that the SD process does not necessarily raise ACA. The passage bridging pages 307 and 308 discloses the SD treatment of IVIG (intravenous immunoglobulin) preparations and compares the product with non-SD-treated IVIG. See page 308, first complete sentence:

"The results of this study show no evidence of serious adverse events with any of the products infused and no statistical difference in the rate of mild reactions after infusion."

If the SD process had raised the ACA of IVIG to clinically unacceptable levels, which is the supposed problem addressed in the patent, there would certainly have been a difference in the SD-treated and non-SD-treated products.

Hence, sections 2.2 and 2.4 of the proprietor's response do not answer our point in relation to D4, namely that the claimed process is not inventive: the claim purports to cover processes in which no problem is solved in an inventive manner, because there is no problem in the first place.

2.9.2. The proprietor's criticisms of D4 indicate that the claim should be restricted

The proprietor (sections 2.4 and 2.5) has criticised our D4 evidence on the basis that (i) the D4 process used a CM Sepharose column (i.e. cation exchange chromatography) to remove the solvent and detergent (whereas the examples of the patent use filtration, diafiltration and hydrophobic chromatography) and (ii) the D4 experiments used two detergents (whereas the examples of the patent use just one). The implication seems to be that therefore one would not expect the initial steps of the D4 process to raise ACA. Nevertheless, the claim purports to include a process that involves cation exchange chromatography and an SD step that involves two detergents. The proprietor has nicely underlined our point: the claim seems to cover processes in which the ACA is not raised and therefore, if it does have such a scope, then it covers processes in which the "invention" serves no technical purpose. Put slightly differently, if it is (for example) the use of hydrophobic chromatography in the proprietor's process that gives him the supposed problem of raised ACA in the absence of aggregates, then his claim should be restricted to processes that employ hydrophobic chromatography. Those in this field who use an SD-based process that does not raise ACA (or

which raises ACA and causes aggregates which, as the proprietor has acknowledged, were known to be removable by a low pH and low ionic strength incubation) should be free to use their SD process and to follow it up with a D2-type incubation. They should not be inconvenienced by this specious patent,
 5 which (at most) addresses only the self-inflicted problems caused by the proprietor's particular process.

2.9.3. D4 does show that the claim covers processes in which the "problem" is not solved.

10 In Section 2.3 of the response, the proprietor states that our D4 experiments showed "undesirably high ACA levels both with and without SD treatment". In fact, the ACA levels reported in D4 were not undesirably high; they are below the maximum permitted in the European Pharmacopoeia, the relevant part of which we enclose as D9. More specifically, the limit for ACA (D9, page 1745, first entry in Col.2) is 1 CH₅₀/mg Ig (i.e. 50 CH₅₀/50 mg Ig), whereas the levels
 15 reported in D4 were both only 45.6 CH₅₀/50mg Ig.

Hence, D4 does indeed show that there are processes within Claim 1 in which the "problem" that is addressed by the patent (namely "unacceptably high levels of ACA"; see Patent, p.2, lines 38-39) is simply not encountered. Clearly, if there is
 20 no problem, then the claimed subject matter cannot represent a solution to a problem.

The *further* reduction of ACA and *maintenance* of an acceptable level of ACA were taught in D2.

2.10 IN THE LIGHT OF D17, IT WAS OBVIOUS TO USE A PROLONGED LOW PH INCUBATION IN ORDER TO REDUCE VIRAL TITRE

25 D17 discloses a process for preparing immunoglobulins for intravenous administration, the process comprising a low pH (pH 4.25) incubation for 12 or 24 days. See the right-hand half of Fig. 1 and Table 3. The objective was to reduce viral titre. The ionic strength is not stated. However, it was known from D2 (see especially column 4 lines 33-41) that a low ionic strength was beneficial for
 30 maintaining a low ACA. Hence, the person skilled in the art would have used a low ionic strength when preparing the Ig solution of D17.

It was obvious to combine various sorts of viral inactivation steps in order to reduce viral titre as much as possible. See, for example, D7, in which an SD step is followed (after removal of the solvent and detergent) by a low pH incubation.
 35 Hence, it was obvious to include an SD step (as taught in D7 or D1) in the process of D17. Alternatively, it was obvious to prolong the low pH incubation step of D7 in the light of the teaching of D17 or D2 that incubation/storage at low pH and low

ionic strength was beneficial. Either way, one ends up with the process of Claim 1.

3. ADDITION OF SUBJECT MATTER

3.1 CLAIM 1 SHOULD REFER TO THE MODEL SYSTEM AND TO BVDV IN PARTICULAR

We maintain the position set out in our opposition. In the application as filed, there are only two disclosures of the $4\log_{10}$ feature. The first occurs at page 3, where it is stated that the viral inactivation step "in a model system" (our emphasis) preferably results in a $4\log_{10}$ reduction in the titre of lipid enveloped viruses. At the second location, namely the end of the first paragraph on page 7, the particular model system is disclosed in more detail, namely a combination of HIV-1 and BVDV. It is clear from this second location that, although the model system contained two viruses, it was specifically the inactivation of BVDV, and not the inactivation of HIV-1, that provides the basis for the $4\log_{10}$ feature.

In Claim 1 of the granted patent, on the other hand, there is a disclosure of a generalised process in which the titre of *any and all* lipid-enveloped viruses is reduced by at least $4\log_{10}$. One can easily imagine that the process conditions might need to be different in order to reduce by $4\log_{10}$ the titre of a lipid-enveloped virus that was not BVDV. No such process is disclosed in the application as filed.

Hence, the specific subject matter that was added, in contravention of Article 123(2) EPC, was the concept of a solvent-detergent process that would reduce the titre of any and all lipid-enveloped viruses by at least $4\log_{10}$, rather than just reducing the titre of the BVDV-based model system by at least $4\log_{10}$.

3.2 THE " $4\log_{10}$ " FEATURE IS TECHNICALLY SIGNIFICANT

On page 10 of the response, the proprietor has argued that the limitation in Claim 1 to the reduction of lipid enveloped viruses by at least $4\log_{10}$ does not provide a technical contribution to the subject matter of the invention but merely limits the protection of the claim.

This is inconsistent with the proprietor's submissions in the first paragraph of section 2.6 of his response to the opposition. In the latter location, the proprietor argued that D4 could not be taken as an indication that step (a) of the claim might not increase ACA, because the relevant step in the D4 experiments had not been shown to achieve a $4\log_{10}$ reduction of viral titre. In essence, therefore, in section 2.6 of the response, the proprietor is saying that a solvent-detergent process that achieves a $4\log_{10}$ reduction of viral titre will increase ACA, whereas a solvent-

detergent process that does not achieve a $4\log_{10}$ reduction of viral titre might not increase ACA. Since the whole point of the alleged invention is to reduce the ACA that is allegedly caused by the solvent-detergent process, it can be seen that, according to the proprietor's own submissions, the $4\log_{10}$ reduction in viral titre undoubtedly provides a technical contribution to the subject matter of the claim.

3.3 THE CROSS-REFERENCE TO D1 IS INADEQUATE IN THIS CONTEXT

On page 11 of the response, the proprietor argues that the cross-reference to D1 at page 2, line 3, of the application as filed should be regarded as an adequate basis for the introduction of the $4\log_{10}$ feature in to claim 1, since D1 (at column 4, lines 57 to 62) discloses that the process can be used to obtain a 4log inactivation of virus. For the following reasons, and in the light of the very strict EPO practice concerning Article 123(2) EPC and cross-references to documents (whether "incorporated by reference" or not), the cross-reference to D1 does not provide an adequate basis for this amendment to claim 1.

3.3.1. *The cross-reference is not proper*

According to Appeal Board decision T689/90, a cross-referenced document can provide a basis for a feature to be introduced into a claim only if the cross-reference satisfies the following four part test. Is it clear that

- (a) protection is or may be sought for the feature?
- (b) the feature contributes to solving the problem?
- (c) the feature belongs to the invention/description?
- (d) the feature is precisely defined and identifiable within the disclosure of the cross-referenced document?

The "feature" in question is the use of a solvent-detergent process that reduces by a factor of $4\log_{10}$ the titre of any and all lipid-enveloped viruses.

In answer to the first question of the four part test, it is by no means clear that protection was going to be sought for this feature. Indeed, at the end of the middle paragraph on page 3 of the application as filed, it was stated only that the reduction in viral titre was assessed by reference to a *model* system (which was specified later), not by reference to any and all lipid-enveloped viruses.

In answer to the second question, it is clear that the feature does *not* contribute to solving the problem. The solution to the problem that is set out in the application as filed is an incubation process in order to reduce ACA. Indeed, if the proprietor's submissions in relation to inventive step are correct, then it is the solvent-detergent step that *creates* the problem; it certainly does not solve it.

In relation to the third question, it should be noted that the cross-reference to the D1 document is in the part of the opposed specification that is headed "Background of the Invention". There is no cross-reference to D1 in the "Summary of the Invention" or the subsequent description of specific
 5 embodiments in the present application as filed.

The fourth question in the test is generally taken to mean that, when the reader of the European application looks at the cross-referenced document, he is clearly led to the feature in question. For example, the European application might state that "Any of the adhesives disclosed in document X can be used" and then he knows
 10 that he should look at the parts of X that disclose adhesives. It is clear that the cross-reference to D1 on page 2 of the application as filed does *not* lead the reader to the paragraph towards the end of column 4 of D1, in which a specific reduction of viral titre is disclosed.

According to Decision T689/90, a cross-reference must pass *all four* of these tests in order for the cross-referenced subject matter to be introduced into the European specification without contravention of Article 123(2). As we have shown above,
 15 the cross reference on which the patentee relies does not pass *any* of these tests. Hence, the introduction of the feature contravened Article 123(2) EPC.

3.3.2. *D1 does not disclose the feature anyway*

As noted above, the offending feature in claim 1 is the disclosure of a solvent-detergent process that reduces by at least $4\log_{10}$ the titre of *any and all* lipid-enveloped viruses. Even if the cross-reference to D1 were proper (which, for the reasons explained above, is not the case), the feature still cannot be found in D1. The relevant disclosure in D1 is at column 4, lines 57 to 62. This refers to
 20 "inactivation of virus" and it is clear from the preceding passages that the viruses in question are simply the various *hepatitis* viruses, not any and all lipid-enveloped viruses.

Hence, whether one refers to the legal standard established on T689/90 or to the technical content of D1, it is evident that the cross-reference to D1 does not help
 30 the proprietor.

We therefore maintain the arguments under Art 100(c) EPC that were set out in our notice of opposition.

4. NEW DOCUMENTS SUBMITTED

- D5 Barandun *et al* (1962) *Vox Sang.* 7, 157-174
 35 D6 Prince *et al* (1988) *Proc. Nat. Acad. Sci. USA* 85, 6944-6948

- D7 Eriksson *et al* (1994) *Blood Coag. & Fibr.* 5, S37-S44
- D8 Pehta (1996) *Transfusion Medicine Reviews* X, 303-311
- D9 European Pharmacopoeia 01/2005:0918, pages 1744-1745
- D10 EP 525 502 (Octapharma; Gehringer & Selosse)
- 5 D11 Ng *et al* (1993) *Vox Sang.* 65, 81-86
- D12 Rousell *et al* (1989) *Clinical Therapeutics* 11, 143-150
- D13 US 5 410 025 (Biotest Pharma; Möller & Piechaczek)
- D14 Advertising brochure for "Octagam" IVIG, published by Octapharma, February 1995
- 10 D15 Test results, conducted in August 1995, on "Octagam" IVIG
- D16 Extract from Octapharma's web site, August 2005, giving product information concerning "Octagam" IVIG
- D17 Mitra *et al* (1986) *Transfusion* 26, 394-397

5. CONCLUSIONS

- 15 All of the claims lack an inventive step for a variety of different reasons.

The amendment of Claim 1 to require that the SD step reduces the lipid-enveloped virus level by at least $4\log_{10}$ added subject matter to the application as filed.

The patent should be revoked.

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